REMARKS

I. *Introduction*

Claims 1, 3, 6-12, 14, 16, 17, 19-21, and 28-30 are pending. Claims 1 and 3 have been amended and claims 29 and 30 are new. Claims 2, 15 and 25-27 have been cancelled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Support for the amendments to claim 1 may be found in the specification at least in the paragraph that bridges pages 9 and 10 ("release 3-10 hours following oral administration"); claim 2 ("therapeutic effect over 24 hours"); page 29, lines 4-12 ("delayed release polymer"); and at page 29, lines 23-30 ("solid dosage unit"). Support for new claim 29 may be found in the specification at least in original claim 4; Examples 5 and 6 ("uncoated immediate release tablet" and "a delayed release tablet"); in the paragraph bridging pages 32 and 33 ("25 to 75 mg milnacipran"); and the paragraph bridging pages 27 and 28 "one or more methacrylic acid-methyl methacrylate copolymers soluble at a pH 6.0 or above"). Support for new claim 30 may be found in the specification at least in original claim 4 and in the paragraph that bridges pages 9 and 10 ("Release of the third pulse occurs . . . typically about 5 hours to approximately 18 hours following oral administration."). No new matter has been introduced by way of any of the foregoing amendments to the claims.

II. *Examiner Interview*

The undersigned and the Applicants wish to thank Examiner Schlientz for the cordial and productive interview of May 7, 2009. The Examiner's helpful comments and suggestions were instrumental in preparing this response. During the interview, Applicants' representatives, Collegium representative Alison Fleming, and the Examiner discussed the rejection under 35 U.S.C. § 112, first paragraph (written description). The Examiner stated that the amendments to claim 1 contained herein appeared to overcome that rejection. Applicants' representatives also discussed how the present invention is novel and non-obvious over the art of record. In particular, Applicants' representatives pointed out, that claim 1 is not prima facie obvious over the art of record due, in part, to the recitation of the feature "release[of milnacipran] 3 to 10 hours following oral administration of the formulation." Applicants' representatives pointed out that this feature of the second milancipran pulse clearly requires that the claimed formulation

release milnacipran over the recited period. By implication, this same feature requires that the milnacipran be colonically absorbed throughout a substantial amount of the same period. As set forth in greater detail in Dr. Fleming's declaration under 37 C.F.R. § 1.132 ("the Declaration"), a "release[of milnacipran] 3 to 10 hours following oral administration of the formulation" would be understood by someone with skill in the art as requiring the absorption of a substantial amount of the milnacipran in the delayed release solid dosage unit in the colon (*e.g.*, five hours after oral administration of the formulation). Certainly a release of milnacipran occurring 5 to 18 hours following oral administration of the formulation, as claimed in new claim 30, requires the absorption of a substantial amount of the milnacipran in the delayed release solid dosage unit in the colon.

III. *The rejections under 35 U.S.C. § 103(a) should be withdrawn*

In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of U.S. Patent No. 6,340,476 to Midha *et al.* in combination with Marc Ansseau *et al.*, 114 *Psychopharmacology* 131-137 (1994). In the Office Action, claims 1-3, 6-12, 15-17, and 19-21 have been held obvious over the disclosure of Midha in combination with Ansseau and U.S. Patent No. 6,699,506 to Paillard *et al.* In the Office Action, claims 1-3, 6-12, 14-17, and 19-21 have been held obvious over the disclosure of Midha in combination with Ansseau and Published U.S. Appl. No. 2003/0203055 to Rao *et al.* In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of Midha in combination with Ansseau, Neliat *et al.*, 35 *Neuropharmacology* 589, 592 (1996), and U.S. Patent No. 6,228,398 to Devane *et al.* In the Office Action, claims 1-3, 6-10, 15-17, 19-21, and 25-28 have been held obvious over the disclosure of Midha in combination with Ansseau, Neliat, and U.S. Patent No. 7,008,640 to Watanabe *et al.*

Claim 1, as amended, is directed to a milnacipran formulation that provides pulsatile release of milnacipran. The formulation comprises an immediate release solid dosage unit comprising a first dose of milnacipran that is released substantially immediately following oral administration of the formulation to a patient, resulting in a first plasma level peak at a time between approximately 0.05 hours to less than approximately 3 hours following oral administration. The formulation also comprises a delayed release solid dosage unit comprising a delayed release polymer and a second dose of milnacipran that is released 3 to 10 hours

following oral administration of the formulation. There is a lag time where there is substantially no release of milnacipran between the release of milnacipran from the immediate release solid dosage unit and the release of milnacipran from the delayed release solid dosage unit. Finally, the formulation produces a therapeutic effect over 24 hours when administered to a patient in need thereof with diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation.

Claim 1, as amended, recites two separate releases of milnacipran, the first occurring immediately and the second occurring 3 to 10 hours following oral administration of the formulation. The claim also provides that following the first release, there results "a first plasma level peak at a time between approximately 0.05 hours to less than approximately 3 hours." This language reflects the fact that although the drug is released substantially immediately upon ingestion, absorption of the drug (ie, transfer from the GI tract into the circulatory system) occurs over a period of time following release. Although not explicitly recited, there is likewise an absorption timeframe following the second release at 3 to 10 hours, wherein the drug is present in the GI tract and available for absorption, which occurs for a period of five or more hours.[1] Indeed, for reasons discussed in detail below, even where the second release of the drug occurs early in the claimed range, *i.e.*, near three hours, there will still be absorption of a therapeutically significant amount of the drug for a period corresponding to a time when the drug is in the colonic region of a patient, corresponding to five or more hours. Accordingly, in reciting a 3 to 10 hour release of the second dose, the claim necessarily requires that a significant amount of the milnacipran be absorbed colonically.

As shown in Figure 2 on page 36 of the Keller declaration filed on January 3, 2008 (attached hereto as Exhibit C), the delayed release solid dosage unit begins to release

[1] The absorption period following the first release of milnacipran is shorter than the absorption period corresponding to the second release of milnacipran. Two factors may contribute to the observed difference: (1) disintegration of the dosage form may be faster in the stomach than in lower regions of the GI tract where less water is available to dissolve the formulation; and (2) absorption of the drug will likely be faster in the upper regions of the GI tract than in the lower small intestine and colon due to the relative rates of drug permeation in these regions. (Fagerholm, *Journal of Pharmacy and Pharmacology* 59:905-916 (2007)).

milnacipran such that one observes an increase in the plasma concentration of milnacipran after about 3 hours following the oral administration of the claimed pulsatile formulation. The absorption of milnacipran **must** continue for about another four hours because, as seen in Figure 2 of the Keller declaration, the plasma concentration of milnacipran continues to rise until it peaks after about 8 or 9 hours following the administration of the claimed pulsatile formulation. The claimed pulsatile formulation, therefore, delivers milnacipran for the entire period of 3 to 8 or 9 hours following oral administration of the formulation. This time period is encompassed by the claimed period of 3 to 10 hours following oral administration of the formulation. And, during that period, milnacipran is being absorbed.

At the time the invention was made, one of ordinary skill in the art had a reasonable expectation that after about five hours from ingestion in the fasted state a drug dosage form would be exiting the ileocolonic junction (ICJ) and entering the colon. Ian R. Wilding and David V. Prior, *Therapeutic Drug Carrier Sys. 20*: 405-431 (2003). After about 8 or 9 hours from ingestion of a drug dosage form, under fed or fasted conditions, one would expect the formulation to be in the colon. *Id.* In sum, the claimed pulsatile formulation must deliver a substantial amount of milnacipran to the colon, where the milnacipran is readily absorbed with high efficiency. As discussed in further detail below, this result is contrary to what one with ordinary skill would have expected to observe for a drug as lipophobic as milnacipran.

It is well known that lipo**philic** drugs would be expected to be absorbed well in the colon. It is also well known that lipo**phobic** drugs (*e.g.*, polar drugs) would not be expected to be absorbed well in the colon. *See, e.g.*, S. A. Riley *et al.*, *Aliment. Pharmacol. Ther. 6*: 701-706 (1992) (Exhibit A); P. Artursson, *J. Pharm. Sci. 79*: 476-482 (1990) (Exhibit B); and U. Fagerholm, *J. Pharmacy and Pharmacology 59*: 905-916 (2007) (Exhibit C). Midha, the primary reference on which all of the present rejections rely, teaches formulations that release methylphenidate, a lipophilic drug, in a pulsatile fashion. Devane, like Midha, teaches formulations that release methylphenidate in a pulsatile fashion.

In the Declaration, Dr. Fleming opines that it would appear, from the art cited in the Office Action, that drugs that are well-suited for formulation into a pulsatile release system are those that have a half-life that is less than about three hours and are expected to be absorbed in the lower regions of the GI tract, including the colon. In contrast, at the time the claimed invention was made, one of ordinary skill in the art would *not* have predicted that a

hydrophilic/lipophobic drug such as milnacipran would be effectively colonically absorbed and thus would not have attempted to deliver milnacipran in a pulsed fashion. Midha and Devane disclose that methylphenidate is a drug that is well-suited for formulation into a pulsatile release system for a number of reasons,[2] including the fact that methylphenidate has a short half life. The half life of methylphenidate is 2.1 hours in adults. *See* http://www.mentalhealth.com/drug/p30-r03.html (last visited May 12, 2009). Other drugs that are discussed in the art cited in the Office Action include ketoprofen and ibuprofen. *See* Devane 2:39-3:2. Ketoprofen has a half life of 1-3 hours. *See* Devane 2:41-45. Ibuprofen has a half life of 1.8-2 hours. *See* http://www.healthcareprescriptiondrugabuse.com/Ibuprofen.html (last visited May 12, 2009). As set forth in the Declaration, it is Dr. Fleming's belief that methylphenidate, ketoprofen, and ibuprofen, are lipophilic drugs. *See, e.g.*, http://uuhsc.utah.edu/pharmacy/bulletins/NDB_112.pdf (for methylphenidate); T. Ngawhirunpat *et al.*, *Pharmazie 56*: 231-234 (2001) (for ketoprofen); F.R. Formiga *et al.*, *Int'l J. of Pharmaceutics 344*: 158-160 (2007) (for ibuprofen). In contrast to methylphenidate, ketoprofen, and ibuprofen, milnacipran is highly lipophobic and has a half life that is significantly longer than the half life of the compounds disclosed in the art cited in the Office Action. For example, at seven hours,[3] the half life of milnacipran is over three times longer than that of methylphenidate and over two to seven times longer than the half life for ketoprofen. Accordingly, in the Declaration, it is Dr. Fleming's opinion, at least because milnacipran has a relatively long half life and is lipophobic in nature, that one of ordinary skill in the art would have had no reason to employ a drug such as milnacipran in a pulsatile release system as claimed.

It is also Dr. Fleming's opinion, as set forth in the Declaration, that the prior art does not render the claimed formulation obvious even if there would have been a reason to formulate milnacipran into a pulsatile release system. As set forth above, the recitation in the claim of release at three to ten hours following administration means that the drug is absorbed during the period in which it is in the colonic region. However, at the time of the present invention, one of

[2] Other reasons include the fact that methylphenidate has a potential for tolerance (loss of clinical efficacy when constant blood levels are maintained) and potential for abuse. *See* Midha 2:39-43. To my knowledge, milnacipran does not share these features with methylphenidate.

[3] http://www.answers.com/topic/milnacipran (last visited May 12, 2009).

ordinary skill in the art would not have had a reasonable expectation of success of obtaining a pulsatile formulation of a drug having the chemical and pharmacokinetic properties of milnacipran that a) provides a release spectrum where the milnacipran is released 3 to 10 hours following oral administration of the formulation; b) provides an absorption spectrum where a substantial amount of the milnacipran that is released is very efficiently absorbed in the colon; and c) provides a release profile that results in therapeutically effective plasma levels over approximately 24 hours.

According to the Declaration, one of ordinary skill in the art would have had a reasonable expectation that a lipophilic drug such as Midha's methylphenidate, would be colonically absorbed. Accordingly, the skilled artisan would have been motivated to produce the pulsatile drug dosage form taught by Midha to deliver a lipophilic drug that is absorbed as far down the gastrointestinal tract as the colon. But the person of skill in the art would not have had a reasonable expectation that a drug such as milnacipran, which is highly lipophobic, would be colonically absorbed and certainly not as well as the inventors observed.

At the time the claimed invention was made, one of ordinary skill in the art would *not* have predicted that a hydrophilic/lipophobic drug such as milnacipran would be effectively colonically absorbed. Instead, the skilled artisan would have wanted to release a drug as hydrophilic/lipophobic as milnacipran relatively quickly because it is well known that lipophobic drugs like milnacipran are absorbed best in areas of the higher gastrointestinal tract (*e.g.*, not as far down the GI tract as the colon).

In sum, therefore, the prior art, including Midha and Devane, does not provide a reasonable expectation of success that a highly lipophobic drug such as milnacipran could be fully absorbed by the human body when colonic absorption is required according to the profile claimed for the delayed release solid dosage unit, *i.e.*, 3 to 10 hours following oral administration of the formulation. Accordingly, the claimed composition is not *prima facie* obvious over the art of record. Reconsideration and withdrawal of all of the obviousness rejections are therefore respectfully requested.

IV. *Some of the art of record, namely Paillard, discourages the slow release of milnacipran*

Paillard teaches multiparticulate, extended release milnacipran formulations. Paillard makes no mention of delayed release milnacipran formulations. Further, a close reading of

Paillard reveals that he discourages the skilled artisan from releasing milnacipran slowly from a dosage form. All of Paillard's formulations, with the exception of three, release (*in vitro*) between 10 and 55% of the dose in 2 hours, between 40 and 75% in 4 hours, between 70 and 90% in 8 hours, and between 80 and 100% in 12 hours. And Paillard identifies the three formulations in examples 6, 8, and 9, which do not release between 10-55% of the dose in 2 hours, as "not mak[ing] it possible to achieve the abovementioned objective in vitro." Paillard at 12:41-45; 14:63-67; and 16:34-38. In sharp contrast, the claimed pulsatile release formulation comprises a delayed release solid dosage unit comprising a delayed release polymer. Representative *in vitro* dissolution profiles for formulations encompassed by the instant claims is shown in Figure 1 of the on page 36 of the Keller declaration filed on January 3, 2008. None of those formulations releases more than 10%, let alone 55% in two hours. Only one of those formulations ("lot #6"), in fact, releases about 10% in 4 hours. In short, the delayed release solid dosage unit portion of the claimed pulsatile release formulation is significantly different than Paillard's extended release milnacipran formulation. That Paillard discourages the slow release of milnacipran is consistent with the wisdom at the time the claimed invention was made. One of ordinary skill in art at the time the claimed invention was made would have wanted to release a drug as hydrophilic/lipophobic as milnacipran relatively quickly (*e.g.*, 10-55% in the first two hours) because they would have known that lipophobic drugs like milnacipran are absorbed best in areas of the higher gastrointestinal tract (*e.g.*, not as far down the GI tract as the colon). To the extent that Paillard's teachings could be applied to reject the claimed formulation as obvious, Applicants assert that Paillard actually teaches away from any such formulation.

Applicant respectfully submits that the pending claims are in condition for allowance. The Examiner is respectfully urged to contact the undersigned telephonically if she believes that it will expedite the allowance of the pending claims.

Respectfully submitted,
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Dated: May 13, 2009

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